

Larynx Preservation Rate in Laryngeal Cancer Patients Treated with Chemotherapy and Radiotherapy: An Institutional Review of 250 Patients

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ABSTRACT

Introduction: Chemo-radiation preceded by induction chemotherapy is reported valuable alternative to laryngectomy in laryngeal cancer for larynx preservation. This study was performed to assess the influence chemo radiation on preservation of larynx.

Materials and Methods: Two hundred and fifty sequential patients treated from January 2012 to December 2012 in our institute were reviewed and who were available for follow-up in this retrospective study. Total dose of 66-70 Gray was used at 2 gray per fraction daily for five days week were used. Larynx preservation rate at 3 years of median follow-up were analyzed.

Results: Among 250 patients, larynx preservation was possible in 170 patients (68%). With chemo-radiation, excellent preservation of larynx was achieved in stage II (78%) disease, while in advanced stage III and stage IVA, larynx preservation was 67.06% and 64.35%, respectively.

Conclusion: Chemo-radiation (either neoadjuvant chemotherapy followed by chemo-radiation or concurrent chemo-radiation) has better larynx preservation rate in early as well as advanced laryngeal cancer patients.

INTRODUCTION

Cancer larynx incidence in India is 3.2 per lakh male and female per year. The number of deaths is 1.1 per lakh male and female per year. These were age-adjusted and based on 2008-2012 cases and deaths.¹ Total laryngectomy can provide disease control in locally advanced cancer larynx patients and thus having negative impact on patient quality of life.

Organ preservation strategies started in the early 80's with initial trials demonstrating the potential of

chemotherapy to cause tumor regression as well as predict response to radiotherapy.² since, then it is used in conjunction with radiotherapy as an approach to organ preservation in various combinations as sequential neoadjuvant and concurrent.

The Veterans Affairs (VA) Study group was pivotal for establishing the role of larynx preservation in advanced laryngeal cancers. In this study, patients were randomized to the experimental group of induction chemotherapy (ICT) followed by radiotherapy in those with partial response against the standard of care i.e. surgery followed by adjuvant radiation and they were able to achieve larynx preservation in 64% maintaining similar overall survival in both arms. This study set the stage for further larynx preservation studies and established induction chemotherapy as standard of care.³

In the 1990s, Forastiere et al. conducted a three armed study comparing induction chemotherapy, concurrent

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chemoradiotherapy (CCRT) and radiotherapy alone in patients with advanced laryngeal cancers.⁴ Overall survival was comparable in all the three arms, larynx preservation was best with concurrent CRT. Two year larynx preservation rates of 88%, 75% and 70% in the CCRT, induction arm and radiation alone arm. This was further supported by the meta-analysis of chemotherapy in head neck cancer which demonstrated an absolute benefit of chemotherapy administered concomitantly.⁵

10 year update of Radiation Therapy Oncology Group 91-11 studied into the long-term effect in these approaches.⁶ Radiotherapy alone was significantly inferior to both induction chemotherapy and concurrent chemo radiotherapy arms. With regards to toxicity, mortality not related to cancer or treatments were significantly higher in concurrent chemotherapy group (30.8% vs. 20.8% in the induction chemotherapy group versus 16.9% in radiotherapy alone group). It could be attributed to late toxicity related to swallowing dysfunction along with silent aspiration.⁷ Long-term interpretation of speech and swallowing showed acceptable results although available data was limited.

Chemoradiation preceded by induction chemotherapy is reported valuable alternative to laryngectomy in laryngeal cancer for larynx preservation. This gave us the impetus to evaluate larynx preservation rate in our institute.

MATERIALS AND METHODS

Actually total patient reviewed were 310 patients out of which sixty patient's data were not available for analysis so we have assessed only 250 patients. Two hundred and fifty sequential patients treated from January 2012 to December 2012 and who were available for follow-up in our institute were reviewed in this retrospective analysis. All patients were of stage II, III, IV Laryngeal cancer and were treated with curative intent by combined chemo-radiotherapy. Inclusion criteria were histology of squamous cell carcinoma (SCC) of supraglottic larynx with no prior radiation or surgery for head and neck cancer, Karnofsky Performance Status (KPS) more than or equal to seventy and age more than or equal to 18 years with no medical comorbidity. Exclusion criteria were Stage I supraglottic cancer, glottic and subglottic cancers, prior radiation and surgery done for oral cancer, other than squamous cell carcinoma histology, KPS less than 70 years, age less than 17 years and thyroid cartilage involvement. Detailed analysis of pretreatment work included complete history, thorough physical exam including loco regional examination of disease, indirect laryngoscopy, direct laryngoscopy, cytology, and biopsy.

Baseline and metastatic investigations like complete blood count, blood biochemistry and radiographic examination

including X-ray chest, X-ray soft tissue neck, and CT scan of head and neck were done. All patients had undergone dental checkup prior to chemo-radiation, and in patients who had undergone dental procedure, a minimum gap of 2-3 weeks was given before beginning of radiotherapy. The patients were staged as per AJCC staging manual 2010.

Every patient was reviewed by the multi-disciplinary team, which consisted of radiation oncologist, surgical oncologist and medical oncologist. Chemo-radiotherapy organ preservation was offered after pre-treatment discussion with the patient and the family. Induction chemotherapy was given to the patient with large, fixed neck nodes and bulky primary disease in whom very less air space present inside larynx and on giving radiotherapy they may require emergency tracheostomy.

The organ preservation protocol comprised of Induction Chemotherapy followed by CCRT or upfront CCRT. Every cycle of ICT consisted of cisplatin (75 mg/m²) on Day 1 and 5-fluorouracil (5-FU) (750 mg/m²) infused intravenously (i.v.) on Days 1,2,3,4 and docetaxel (75 mg/m²) i.v. on Days 1. Response evaluation was done at week eight after two-three cycles of ICT. Responder in which there was more than 50% reduction at the primary site and neck, were taken up for definite CCRT while for non-responder surgical treatment was given. Six cycles of concurrent chemotherapy (cisplatin 40mg/m²) was given with radiation. Radiotherapy was given five days per week under conventional radiation schedule at 2 Gray per fraction. Curative doses of 66-70 gray were given for primary site and lymphadenopathy (more than 1 cm) and 50 Gy for the elective neck node. Total dose to the larynx in case of upfront chemo-radiation was 70 gray in 35 fractions, after 46 gray off cord was done and after 60 gray boost was planned to the gross tumor volume while in cases where neoadjuvant chemotherapy was given total dose was kept 66 gray in 33 fraction, after 46 gray off cord was done and after 60 gray boost was planned to the gross tumor volume to a dose of 6 gray. This decrease in dose was due to the poor tolerance because of neoadjuvant chemotherapy they have received prior to radiation. Linear accelerator using six megavoltage x-rays, using two dimensional techniques with parallel opposed beams was used for radiotherapy by using oncentera treatment planning system (Figure 1).

Thermoplastic mask or cast was used for immobilization in all the patients. Initially, the radiation portals encompassed primary disease, involved lymph nodes and microscopic disease around primary and in clinically uninvolved lymph nodes. Superior border of the lateral portal was placed at lower margin of the ala nasi to lower edge of tragus, inferior border at lower margin of the clavicle. Anterior border is along the vertical line joining the anterior end of the zygoma to the junction of the first and second

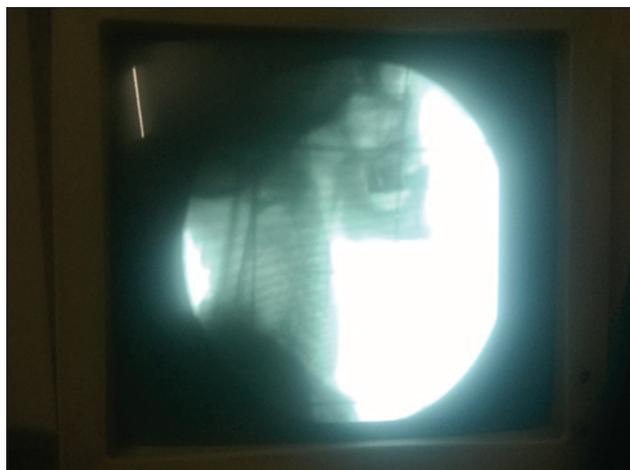


Figure 1: Skiagram showing 2D portal for laryngeal cancer patient

molar and posterior border at the spinous process. After delivering 46 Gy in 23 fractions, the posterior neck field was reduced to spare spinal cord. Last 6 Gy boost was given to involved primary sites with primary echelon and involved lymphnodes (only gross disease). The primary goal of this study was to assess the influence of curative chemoradiotherapy on laryngeal preservation at 3 years of median follow up. It was an objective analysis, and disease-free larynx with grade 0 or grade I hoarseness and satisfactory swallowing function have been considered as functional preservation of larynx. Absence of CR (complete response) or more than grade I hoarseness (unsatisfactory speech) is considered as failure of laryngeal preservation.

For statistical analysis, data was arranged in excel format and was converted to SPSS format version 16 for computing 2-3 year laryngeal preservation.

RESULTS

Patient Characteristics

In this retrospective analysis, age of the patients ranged between 22 and 84 years with median age of presentation being 58 years. There were 238 males (95.20%) and 12 females (4.8%). All patients were of cancer supraglottic out of which 50(20%) were of stage II, 85(34%) were stage III and 115(46%) were stage IV (Table 1).

66 (26.4%) patients received induction chemotherapy and rest of other patient received concurrent chemo-radiation or radical radiotherapy alone. Most of the patients were smokers (220/250).

Laryngeal Preservation Rate

At a median follow up of 3 years for 250 patients who were available for follow-up, overall laryngeal preservation was observed in 170 patients (68%). Larynx preservation

Table 1: Patient characteristics

Characteristics	Number (%)
Age	
21-30	2 (0.8)
31-40	8 (3.2)
41-50	61 (24.4)
51-60	94 (37.6)
61-70	47 (18.8)
71-80	30 (12)
81-90	8 (3.2)
Gender	
Male	238(95.2)
Female	12 (4.8)
Stage	
II	50 (20)
III	85 (34)
IV	115 (46)

Table 2: Stage-wise 3 year laryngeal preservation rate

Stage	Number (%)
II	39/50 (78)
III	57/85 (67.06)
IV	74/115 (64.35)
Total	170/250 (68)

of upto 78% was observed in stage II and in stages III, IV it was 67.06% and 64.35%, respectively (Table 2). Among 238 males, larynx was preserved in 162 patients, while in females out of 12 patients, larynx preservation was possible in 8 patients. Among 220 smokers, larynx was preserved in 149 patients, and out of 30 non-smokers, larynx preservation was possible in 21 patients.

DISCUSSION

Larynx cancers account for nearly 1% of all malignancies and approximately 25% of head and neck tumors. Glottic cancers are approximately 3 times more common than supraglottic tumors; tumors of the subglottic larynx are rare, accounting for approximately 1% to 2% of carcinoma larynx. In India, the situation is converse, where supraglottic cancer is more common than glottic cancer.⁸ Therefore we decided to analyze only supraglottic cancer in this retrospective analysis.

Usually the laryngeal cancer patients median age of presentation is 65 years and less than 4% of our patients are younger than 45 years old and it is seen predominantly in male population.⁹ Approximately two thirds of patients with laryngeal cancer have their disease limited to the laryngeal structures and less than 10% present with distant metastases at presentation.⁹ In our study, median age of presentation is 58 years and 95.20% of patients were males.

Majority of laryngeal cancer patients are now treated with organ preservation protocols. The treatment objective for early laryngeal cancer that can be treated with surgery or radiation, is to obtain cure with functional larynx with least morbidity. Treatment emphasizes avoiding combination of surgery and radiation because preservation of larynx may be compromised. There is no one treatment that has proven to be superior with regard to all treatment goals.^{10,11,12} Radical radiation is as effective as radical surgery in early stage with added advantage of larynx preservation. In most centers, upfront radiation is preferred for T1 and T2 tumors, with surgery being reserved for salvage although hemilaryngectomy produces similar cure rates for selected T1 and T2 laryngeal cancers; irradiation is usually associated with better quality of voice.^{13,14} In 1974, Bataini and colleagues published an overall loco regional control rate of 76% for relatively large series patients with T1, T2, N0-2 supraglottic carcinomas treated by radiotherapy alone.⁹ In our study, 3 year larynx preservation rate in stage II is 78%.

Locally advanced laryngeal cancers (stages III and IV) require radical surgery followed by external radiotherapy. Chemo-radiation is an active alternative for surgery when organ preservation is desired. The landmark trial conducted by VA group established ICT followed by radiotherapy as an alternative to radical surgery for advanced carcinoma larynx. RTOG 91-11 study showed organ preservation was finest achieved with CCRT.^{3,4} In our study, we have found that overall larynx preservation of 68% could be achieved with chemo-radiotherapy (neoadjuvant chemotherapy followed by chemo-radiotherapy, concurrent chemo-radiotherapy and radiotherapy alone which formed a very few number of patients) as the sole treatment modality in patients of stage II-IVA laryngeal cancer. In our study 3 year larynx preservation rate in stage III and stage IV were 67.06% and 64.35 % respectively. When compared with RTOG 91-11, our study does not show inferior results.

Study conducted by Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC), Head and Neck Tumor Study Group had to be prematurely abandoned due to a strong patient preference for organ preservation over surgical resection.¹⁵

In the study by Forastiere et al, chemotherapy-based regimens decreases distant metastases and results in improved disease-free survival (DFS) than radiation alone. At 2 years, 91% were metastases-free in induction chemotherapy followed by radiation arm, 92% were metastases-free in concurrent chemo radiation arm, 84% in the radiation alone arm. Local control rates were 64%, 80%, and 58% in the induction chemo followed by radiotherapy, concurrent chemo-radiation, and radiotherapy alone arm, respectively. Loco-regional control (LRC) was significantly improved in CCRT group, but there was no significant

difference between radiotherapy alone and ICT followed by radiation group.⁴ In our study, local control rate in stage III is around 67.06% and in stage IV, it is found to be 64.35%, which is quite impressive when compared to western literature. When we have analyzed the pattern of failure of preservation of larynx in our patients, out of 80 patients, in whom laryngeal preservation was not possible, 50 had local failure and 30 had local as well as nodal failure.

It is important to remember that, in addition to showing the advantage of using chemotherapy with radiation, RTOG 91-11 trial also demonstrated that radiotherapy alone is a reasonable treatment option for patients who cannot tolerate chemotherapy. In addition, it is critical to remember that the benefits of adding chemotherapy must be waived by the higher rates of treatment related sequelae, some of which can be life-threatening. The benefit of concurrent chemoradiation may reduce in patients older than 70 years.⁵ Given that these patients are at greatest risk of toxicity, the use of chemotherapy in these patients needs to be further investigated. In our study, 15.2% of patients were above 70 years of age where radiation alone is a viable option for larynx preservation.

Intensity modulated radiotherapy (IMRT), a new RT technique, has the advantages of precise delivery, target conformity and normal tissue sparing. It is able to achieve a very high rate of locoregional control with less morbidity under optimal target delineation, appropriate physical quality control and accurate patient setup.¹⁶

CONCLUSION

Our study concluded that chemo-radiation (either neoadjuvant chemotherapy followed by chemo-radiation or concurrent chemo-radiation or radiation alone) has better larynx preservation rate in early as well as advanced laryngeal cancer patients. Quality of life is much improved in patients treated by nonsurgical approach and hence our study's preliminary results were very motivating and gave us the impetus to continue the same protocol for future.

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